N-Myc and GCN5 regulate significantly overlapping transcriptional programs in neural stem cells.

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Public Summary:
Here we examine the functions of the Myc cofactor and histone acetyltransferase, GCN5/KAT2A, in neural stem and precursor cells (NSC) using a conditional knockout approach driven by nestin-cre. Mice with GCN5-deficient NSC exhibit a 25% reduction in brain mass with a microcephaly phenotype similar to that observed in nestin-cre driven knockouts of c- or N-myc. In addition, the loss of GCN5 inhibits precursor cell proliferation and reduces their populations in vivo, as does loss of N-myc. Gene expression analysis indicates that about one-sixth of genes whose expression is affected by loss of GCN5 are also affected in the same manner by loss of N-myc. These findings strongly support the notion that GCN5 protein is a key N-Myc transcriptional cofactor in NSC, but are also consistent with recruitment of GCN5 by other transcription factors and the use by N-Myc of other histone acetyltransferases. Putative N-Myc/GCN5 coregulated transcriptional pathways include cell metabolism, cell cycle, chromatin, and neuron projection morphogenesis genes. GCN5 is also required for maintenance of histone acetylation both at its putative specific target genes and at Myc targets. Thus, we have defined an important role for GCN5 in NSC and provided evidence that GCN5 is an important Myc transcriptional cofactor in vivo.

Scientific Abstract:
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